Sodium butyrate promotes generation of human induced pluripotent stem cells through induction of the miR302/367 cluster.

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Public Summary:
Small molecules can greatly enhance the efficiency of induced pluripotent stem (iPS) cell generation, but the mechanisms by which they act have not been fully explored. We show here that a cocktail of three small molecules significantly promotes iPS cell generation from human fibroblasts. Our data indicate that the small molecule cocktail substantially upregulates the production and stability of a specific microRNA cluster, miR302/367. Collectively, our findings suggest that the small molecule cocktail promotes reprogramming at least partly through the induction of the miR302/367 cluster expression. Further insights into this process may pave the way for the generation of iPS cells using only small molecule cocktails.

Scientific Abstract:
Small molecules (SM) can greatly enhance the efficiency of induced pluripotent stem (iPS) cell generation, but the mechanisms by which they act have not been fully explored. We show here that an SM cocktail (NaB, PD03259, and SB431542) significantly promotes iPS cell generation from human fibroblasts, and NaB is more potent than the other two common histone deacetylase inhibitors (valproic acid and Trichostatin A) in promoting cellular reprogramming. Our data indicate that the SM cocktail substantially upregulates the miR302/367 cluster expression by increasing the stability and transcriptional level of this microRNA (miRNA) cluster in a manner dependent on the four defined transcription factors (TFs). Among the four TFs, Oct4 in particular appears to be required for the induction of the miR302/367 cluster by the SM cocktail. We also found that NaB alone can enhance the TFs-dependent upregulation of the miR302/367 cluster. Using a promoter reporter assay, we show that the SM cocktail remarkably enhanced the transcriptional activity of the four TFs in the miR302/367 promoter. Notably, attenuation of miRNA302/367 using a miRZip impairs the ability of the SM cocktail in promoting reprogramming. Collectively, these findings suggest that the SM cocktail promotes reprogramming at least partly through the induction of the miR302/367 cluster expression. Further insights into this process may pave the way for the generation of iPS cells using only SM cocktails.